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Granular cell tumor of the Vulva: Review of the Literature

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ABSTRACT

Background: granular cell tumors (GCTs) are a rare soft tissue tumor originating from Schwann cells typically located on the neck and head. Cases affecting the vulva are exceedingly rare, with the currently available literature primarily in case report form.

Objectives: the present review of published cases aims to evaluate prognostic factors, management and out-come of vulvar GCTs.

Body: systematic review of the Medline database returned 143 cases of GCTs affecting the vulva.

Patients presented at a mean age range of 30-50 years with a firm, mobile, asymptomatic, small, painless, slow-growing subcutaneous vulvar mass, rarely showing pruritus and ulceration.

Tumor histology is consistent with that of neural tumors and typical granular cell tumors. S-100 proteins, vimentin, and enolase immunostains are frequently utilized in histopathological workup.

Surgical management was the unanimous first-line therapy with wile excision and negative edges. 2% of cases are malignant and, in these cases, outcome is usually fatal. Recurrence occurred within 2 years, in 8% of patients. Follow-up consists in clinical and imaging evaluation.

Conclusion: GCTs affecting the vulva are extremely rare. Malignant GCTs are highly aggressive neoplasm. After surgery, both malignant and benign cases need to follow-up to avoid recurrence.

Keywords: vulvar GCT, Abrikossoff tumor, granular cell myoblastoma

SOMMARIO

Introduzione: il tumore a cellule granulari (GCT) è una rara neoplasia dei tessuti molli che origina dalle cellule di Schwann. Generalmente si localizza nella regione del collo e della testa. I casi che interessano la vulva sono estremamente rari, e la letteratura riporta principalmente case report.

Obiettivi: la presente review dei casi pubblicati si propone di valutare i fattori prognostici, la gestione e gli esiti del GCT vulvare.

Corpo: la review sistematica del database Medline permette di individuare 143 casi di GCT che interessano la vulva.

Le pazienti presentano un'età media compresa tra i 30-50 anni. Il tumore si manifesta come una massa sottocutanea, solida, non dolente, a crescita lenta e, genericamente, asintomatica, mostrando raramente prurito ed ulcerazioni.

Da un punto di vista istologico i GCT vulvari manifestano le tipiche caratteristiche dei tumori neurali e di quelli con cellule granulari. La diagnosi si avvale della positività all'immunoistochimica per la proteina S-100, la vimentina, e l'enolasi.

La terapia unanimemente riconosciuta come gold-standard è l'ampia escissione chirurgica con margini negativi. Nel 2% dei casi i GCT possono essere maligni e, in questi casi, l'esito è solitamente fatale. La recidiva si verifica nell' 8% dei casi entro 2 anni. Il follow-up consiste nella valutazione clinica e radiologica.

Conclusioni: I GCT che interessano la vulva sono estremamente rari. I casi maligni sono altamente aggressivi. Dopo l'intervento chirurgico, sia i casi maligni che i casi benigni necessitano di follow-up per evidenziare eventuali recidive.

Parole chiave: GCT vulvare, tumore di Abrikossoff, myoblastoma a cellulare granulari

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Granular cell tumor (GCT) is a rare neoplasm resulting from swhann cells[1], also known as Abrikossoff tumor. At the beginning, it was described by the russian pathologist (1926) as a tumor arising from striated muscle cells[2]. So it was defined initially "granular cell myoblastoma"[3].

LOCATION

More frequently the GCTs are located in the skin, subcutaneous or submucosal tissue of the head and neck regions, especially at the level of tongue and oral cavity. Less frequently, they can also be found in other anatomic sites as extremities, genitals and visceral organs[4].

Vulvar involvement is found in 5-16% of cases[5]. The most frequent localization is the labium majus[6]. More rarely GCTs are diagnosed in uterus, cervix, ovary, vagina, episiotomy scar and pubis[7-8].

In 25% of cases the lesions are multifocal[9], so clinical examination should include exploration of the total body as well as the genital lesions, especially in the most frequent localization regions[10]. In addition a pre-operative whole body or pelvic imaging could be recommendend.

SEARCH STRATEGY

Currently, all data on vulvar GCT is found in "case report and literature review" form.

A literature search was performed using MEDLINE database from 1951 to 2017; the following search terms were used for the scope of this review: vulvar GCT, Abrikossoff tumor, granular cell myoblastoma.

MEDLINE search returned 63 relevant articles. Included studies were original studies discussing the clinical course (including presentation, diagnostic workup, treatment, and outcome) of patients with GCT affecting the vulva: 62 were case report or reported series and 1 was a literature review. Studies were excluded if not of primary human subjects. (**Table 1**)

EPIDEMIOLOGY

GCT may occur in patients of all age, gender and race, but the literature reports more frequently in black women with greater incidence in the fifth decade of life[11].

Some authors have reported rare cases of family multiple injuries, benign or malignant. This suggests that some patients may have a genetic predisposition to the GCTs[12-13].

CLINICAL PRESENTATION

They generally present as asymptomatic, small, painless, slow-growing subcutaneous nodules, occasionally itching related[6].

Due to non-specific symptoms, it is mandatory to analyze the histological findings[14].

HISTOPATHOLOGIC EVALUATION

Most GCTs are benign but the literature reports 1-7% of malignant cases associated with multiple lesions and regional or distant metastases[15]. In these cases they are highly aggressive disease and can be fatal[16].

According to a review by Kardhashi et al.[13], in 2% of cases the GCT of the vulva is malignant, aggressive and resistant to chemotherapy and radiation treatment[17].

The malignant potential can be predicted by the presence of a lesion larger than 4 cm, rapid growth, recurrence, invasion into adjacent tissues, distant metastasis, older age, female gender[18].

The histological diagnosis of GCT presents specific histological findings[19]. The cells appear large and polygonal or round, with a central vesicular nucleus and abundant granular eosinophilic cytoplasm. The granules are lysosomes or a component of the Golgi apparatus, positive for periodic acid-Schiff (PAS) and luxol fast blue, and resistant to diastase, indicating the presence of myelin inside the tumor. The overlying epithelium may show pseudoepitheliomatous hyperplasia[20].

Most GCTs are positive for S-100 proteins (98%) and CD57. They are also strongly positive for neuron-specific enolase (100%) and vimentin, and the presence of myelin associated glucoprotein has been demonstrated. The proliferation-index with Ki67 and immunostaining for p53 overexpression were significantly higher in atypical and malignant tumors as compared to benign tumors[7].

To classify GCT in benign, atypical and malignant, in 1998 Fanburg-Smith spotted six histological criteria: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (> 2 mitosis / 10 high power fields to 200x magnification), high nuclear to cytoplasmic (N: C) ratio, and pleomorphism. The lesion is defined as

malignant when it shows three characteristics of six, as atypical with two out of six, as benign if there is only the pleomorphism[21].

Fanburg-Smith defined as negative prognostic factors: the age of the patient, the larger size of the tumor, the local recurrence, the presence of metastasis, the histological classification as malign, the presence of necrosis, increased mitotic activity, spindling of cancer cells, vesicular nuclei with large nucleoli.

DIFFERENTIAL DIAGNOSIS

Using an optical microscope, the differential diagnosis from other tumors as well as from melanoma, leiomyoma, leiomyosarcoma, rhabdomyosarcoma, dermatofibrosarcoma, alveolar soft part sarcoma, angiosarcoma, fibrous histiocytoma, and ameloblastoma, can be diffcult[22].

So malignant lesions should be suspected due to their clinical features and confirmed by histological findings and immunohistochemistry that is a useful diagnostic tool for the differential diagnosis[19, 23].

Sometimes the GCT of the vulva can be confused with other lesions such as sebaceous cysts[24], lipomas, fibromas, idroadenomi, papillomas. If there are ulcerations, it is mandatory to perform a differential diagnosis of neoplastic lesions or syphilitic[13]. Immunohistochemistry showed the presence of cell cycle regulatory proteins in some genital carcinomas[25]. The vulvar GCT stain positive for S100 protein, and neuron specific enolase. Ki-67 immunopositivity is shown in 30% of the cell population in malignant tumors.

MANAGEMENT AND OUTCOME

Surgical treatment of GCT is the gold standard. Excision should be wide to ensure negative edges and reduce the risk of recurrence. If the margins are included, the excision should be further developed[24, 26-28]. The GCT has poor response to radiotherapy and chemotherapy; it should be considered in cases where complete excision cannot be achieved[1, 6, 13].

In case of labium majus localization, a complete excision with free margins can be easily performed. The excision of the clitoral, perineal and perianal location may be more difficult or associated with complications such as bleeding, injures and scars.[17].

Regardless of the benign or malignant nature of the lesion, all patients should undergo folow-up after surgical excision[29]. Follow-up should include genital and extragenital clinical examination and, in case of recurrence, imaging evaluation. Biopsy of new eventual lesions should be performed and a second surgical teatrment should be carried out[17].

Malignant GCT may have recurrences or metastases[30]. Local recurrences are related to inadequate excision and occur in 2% of cases in two years[13]. Metastases may occur to regional lymph nodes (lymphatic spread) or lungs, bones and liver (hematogeneous spread)[31]. Regional lymph node dissection should be considered in case of histologic diagnosis of malignancy, although some authors suggest locoregional lymphadenectomy also in presence of atypical lesions[22, 32].

CONCLUSION

The GCTs are rare neural tumors, generally localized on the head and neck, in black female patients, in the fifth decade of life. Rare familial cases have been described. Most GCTs are asymptomatic or shows nonspecific symptoms. Histological examination allows the diagnosis. Benign and malignant forms are described according to the Fanburg-Smith criteria. Immunohistochemistry allows differential diagnosis for GCT in the distinguishing of other forms of cancer. The wide surgical excision is the gold standard treatment. If the edges are positive, a surgical re-excision is required. Malignant forms can show local recurrence or hematogeneous and lymphatic spread. Patients diagnosed with GCT must undergo follow-up to prevent the risk of relaps.

Vulvar localization is rare. The literature describes familial cases. The GCT vulvar can be benign or malignant and they are classified according to the Fanburg-Smith criteria. The malignant forms may recur and surgical treatment is the best possible option.

Table 1.
Titles found in the literature on the topic

Reference (first author)	Patients n	Age	Site and size	Margins	Presentation	Multiple sites	Diagnosis of GCT pre-histology	Follow-up outcome
Rivlin[31] , 2016	1	52	Lt labium majus, 3x3 cm	Margins involved	Asymptomatic	No	No	Reexcision recommended, but the patient refused re-operation. 18-months follow-up, no recurrence
Udasimath Shivakumarswamy[29] 2016	1	65	Lt labium majus, 2,8x2,3 cm	Clear	Asymptomatic	No	No	Patient on follow-up: no signs of recurrence
Sonmez[28], 2016	1	41	Rt labium majus, 1x1x0,5 cm	Margins involved	Asymptomatic	No	No	Reexcision recommended, but the patient refused re-operation. 7-months follow-up, no recurrence
Hee Joo[4], 2015	1	56	2 rt labium majus, 3x1,5 cm and 1x1 cm	Clear				
Vera-Sirera[73], 2014	1	24	Left labium minus, 1,5 cm	Margins involved	Pruritus	Yes: after tongue GCT at 14 years of age, second GCT in vulva	No	15 months follow-up, no recurrence
Kardhashi[13], 2012	1	60	Lt labium majus, 2,5 cm	Clear	Asymptomatic	No		6-year follow-up with no disease recurrence
	1	32	Lt labium majus, 2,8x2,3x1 cm	Margins involved	Asymptomatic, cyst-like formation	No		Ten monthslater two nodular lesions extending to the symphysis pubis,(6.5x4x1.5 cm) Inguinal lymph nodes negative
Hong[1], 2012	1	59	Lt labium majus		slow-growing for nine years	No		Patient on follow-up: no signs of recurrence
	1	23	Rt labium majus	Margins involved	Asymptomatic	No		Subsequently a 3 mm right vulval skin tag excised 5 months after initial surgery, and histology revealed a fibroepithelial polyp. Defaulted after 16 months of follow-up
	1	50	Rt labium majus	Margins involved	Asymptomatic	No		yearly follow-up for 8 years and 1 month, no signs of recurrence
	1	17	Lt labium majus, 2 cm	Margins involved		No		lost to follow-up after 15 months
Zhang[74], 2011	1	27	Lt labium majus 5 cm, rt labium majus 4 cm, lt nympha 5 cm, rt nympha 6 cm	Clear	Pruritus	No		
Mehta[33], 2010	1	55	Rt labium majus, 7 x 5 x 5 cm	Clear	Itching, erosions, colored, since the age of 15 years	Yes, left thigh	No	Not done
Kondi-Pafiti[34], 2010	4	35–38	3 lt, 1 rt, 0.8–1.7 cm	Clear	painless	No	No	1–3 years, no recurrences

Continue...

Reference (first author)	Patients n	Age	Site and size	Margins	Presentation	Multiple sites	Diagnosis of GCT pre-histology	Follow-up outcome
Papalas [10], 2010	13/17 lesions	46	Labia major, 6/17, mean 2.1 cm	1 atypical, 7/17 positive margins	Slow-enlarging, occasionally pruritus, pigmentation	In 3 cases(vulvar andextravulvar)1 case extravulvar	No	7 years, of the 7 patients with involved margins: 5 stable, 2 reexcisions after 14 and 8 years; all negative margins: stable
Torrijos-Aguilar [9], 2009	1	5	Pubis	Margins involved	juvenile xanthogranuloma /dermatofibroma	No	No	
Sargenti-Neto[35], 2009	1	41	Perineal, tongue, lip	Clear	enlarging mass	Yes	No	4 years later new lesions in the groin, vulva and zygomatic region
Laxmisha [36], 2007	1	18	Clitoris 2.5–2 cm	Clear	Slowprogressive, asymptomatic, brownish-black	No	Appendageal tumor	6 months, no recurrences
Levavi[16], 2006	1	61	Rt labia major, 12x6x3 mm	Margins involved	Pruritus	No		Further excision at 3 months – squamous papilloma
	1	47	Rt labia major, 15x10x10 mm	Clear	Asymptomatic	No		
	1	61	Lt labia major, 12x10x7 mm	Clear	Asymptomatic	No		
	1	72	Lt labia major, 20x15x10 mm	Margins involved	Enlarging mass	No		Refused further excision
	1	68	Rt labia major, 20x20x10 mm	Clear	Asymptomatic	No		Died 6 years later from other causes
	1	44	Rt finger, Rtgroin, multicentric vulva, Rt toe	Clear	Enlarging mass	Yes (vulvar/ extravulvar)		Multicentric, metachronous and synchronous lesions
Cheewakriangkrai[5] 2005	1	59	Lt labia major, 3!2 cm	Clear	Asymptomatic Enlarging mass	No	No	Uneventful
Ashokkumar [37], 2004	1	36	Mons pubis 1 cm cystic	Margins involved	Asymptomatic	No	No	Not done
Schmidt[24], 2003	*1*	*55*	*Lt labia major spreading to the mons pubis, fist sized*	*Focally reaching the margins without diagnosis of malignant GCT (no further therapy was performed)*	*Enlarging mass*	*No*	*No*	*After 13 months several newly formed pea-sized vulvar tumors: widespread regional and retroperitoneal metastasis. The patient died of her disseminated disease within 4 months*
Ellison[38], 2003	1	71	Lt labia major 3 cm	Margins involved	Asymptomatic enlarging mass	No	No	Next further re-excision
Díez[18], 2002	1	30	2 rt labium majus, 1 cm and 2 cm	Clear	Itching, pain, colored	No	Biopsy	2 years, no recurrences
Althausen[6], 2000	12/13lesions	52(33–75)	8 labium majus,2 perianal area,1 introitus,1 perineal,0.3–2.3 cm	4 lesions infiltrating the margins	10 enlargingmass, 2 pain,1 pruritis,brown, red,yellow, white	1 patientnew lesionafter13 years		5/8 patients withinfiltrative tumor edge developed recurrence, despite that 3 had previously had negative surgical margins and none in the cases with 'pushing' borders
Ramos[32], 2000	*1*	*17*	*Marble-sized enlarging in 4 cm, Lt labium majus*	*Lesion extended to the surgical margin with diagnosis of malignant GCT*	*Enlarging mass treated with antibiotics*	*No*	*No*	*Left hemivulvectomy and groin lymph node dissection, radiotherapy, without disease at 16 months*

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Reference (first author)	Patients n	Age	Site and size	Margins	Presentation	Multiple sites	Diagnosis of GCT pre-histology	Follow-up outcome
Cohen[39], 1999	1	9	2 cm Lt labium majus	Clear	Enlarging mass for 6 months	No		3 years without recurrence
Fanburg-Smith[21], 1998	*1*	*56*	*1.5 cm*			*No*		
Ortiz-Hidalgo[40], 1997	1	60	3 cm, clitoris	Clear	Enlarging mass for 2 months	No		Not done
Horowitz[7], 1995	*20*	*50 (26–78)*	*18 labium majus, 1 clitoris, 1 perineal, 0.4–12 cm*		*9 enlarging mass, 3 pain, 1 pruritus, 6 incidental, 1 new lesion lung lesion*	*Yes (2 cases)*		*The patient, 32 years old, with a 12-cm single lesion (without histologic features of malignancy) had a recurrence after 67 months and died of pulmonary metastasis after 70 months*
Khansur[41], 1987	1					No		
Chambers[42], 1979	1	56	Lt labium majus, 3 cm		Ulcerated	No	No	
	1	21	Lt labium majus, 2.5 cm		Enlarging mass	Yes	No	
Richter[43], 2006	1	50	Lt labium majus, 1 cm					
Simone[44], 1996	1		1 cm					
Morrison[45], 1987	3							
Hale[23], 2002	1						Diagnosis of a vulvar GCT by fine-needle aspiration biopsy	
Guenther[46], 1993	1	Child						
Murcia[8], 1994	1		Episiotomy scar					
Wolber[47], 1991	7				2 ulceration	1 vulvar		
Dorfman[48], 1990	1							
Raju[49], 1987	2					No	None	
Lomeo[50], 1987	1							
Bonilla-Musoles[51] 1987	2							
Brooks[52], 1985	1	6		Clear				
Rubesin[53], 1985	1					Yes, extravulvar		GCT extravulvar in the patient's mother
Slavin[54], 1986	1		Clitoris		Priapism	No		
Degefu[55], 1984	1		Clitoris, in pregnancy					
Vold[56], 1984	3							
Morris[57], 1982	2							
Zanetta[58], 1981	1	33						
Robertson[59], 1981	*1*				*Metastasis, regional lymph nodes*			
Jones[60], 1980	1							
Lack[61], 1980	4							
King[62], 1979	3				One extravulvar			
Dgani[63], 1978	4							
Hutchins[64], 1977	1							
Màgori[65] ,1973	*1*				*No*			
Gifford[66], 1973	1				Yes (extravulvar)			

Continue...

Reference (first author)	Patients n	Age	Site and size	Margins	Presentation	Multiple sites	Diagnosis of GCT pre-histology	Follow-up outcome
Bruno [67], 1968	1							
Doyle [68], 1968	1							
Musgrove [69], 1964	1							
Rubin [70], 1959	4							
Bishop [71], 1956	1	6						
Sadler [72], 1951	*1*							
Brunel I [75], 2015	1	73						local recurrence 21 months after the surgery
	1	60		Margins involved				second surgery
	1	58		Margins involved				second surgery
Tawfiq N [76], 2013	1	28	14 cm					local surgery, five months later malignant transformation Radiotherapy; after 20 months local recurrence and lung metastasis and chemotherapy symptomatic medical treatment
Asangi R [78] 2013	1	12	3x4 cm		slightly erythematous mass with surrounding granulation tissue, the specimen consisted of a rounded wedge excision of vulvar tissue showing an oval, discolored, raised surface			complete excision

Note: malignant cases are italicized.

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